

TELEPHONIC INTERVIEW OUTLINE

USSN 09/485,245

Hopkins "COMPOSITIONS COMPRISING RANDOM MIXTURES OF NUCLEOTIDES"

2:00 pm EDT Tuesday, May 14, 2002

Examiner Cynthia Wilder, Ph.D. 703-305-1680

1. OUTSTANDING REJECTIONS

- a. Claims 1-5 stand rejected under 35 U.S.C. §103(a) Over Suganuma in view of Shen.
- b. Claim 6 stands rejected under 35 U.S.C. §103(a) over Suganuma in view of Shen in view of Hoeltke.

2. APPLICANT'S INVENTION AND PATENTABILITY ARGUMENTS

a. The Invention and the State of the Prior Art:

- i. The invention relates to an improvement in random priming methods where random sequence oligonucleotides are used to prime DNA synthesis on denatured template DNA at numerous sites along its length. The primer-template complex serves as a substrate for the "Klenow" fragment of DNA polymerase I and radioactive nucleotides are provided such that newly synthesized DNA is made radioactive.
- ii. Various kits containing solutions of oligonucleotides are known for practice of random priming methods. (Stratagene)
- iii. There has been a trend toward using longer primers in solution in order to provide more rapid priming. (Megaprime and Ready-To-Go kits)
- iv. Suganuma suggests that shorter primers might be desired for liquid primer solutions because of self-annealing properties of larger primers in solution.
- v. Dried primer kits were also known for use with 9-mer and higher primers. (Rediprime, BP 298,269 discloses 15-mers and 17-mers) These were not thought to be subject to the problem of Suganuma. Moreover, there still remained a bias preferring longer primers because of the belief that such longer primers would provide more rapid priming than shorter primers.
- vi. The present invention relates to the discovery that there is a self-annealing problem with dried primers and that the solution to that problem is the use of shorter dried primers.
- vii. The present invention is thus directed to dried mixtures of random primers and relates to the discovery that self-annealing occurs when random 9-mers are used in dried predisposed labeling kits. The problem is specific to 9-mers (and longer oligonucleotides) used in dried kits and does not represent a problem with shorter dried primers. *Shorter Primers Only*

b. The Obviousness Rejections under 35 U.S.C. §103(a) should be Withdrawn.

- i. The Obviousness rejections under 35 U.S.C. §103(a) should be withdrawn because (1) the selection of 6-mers to 8-mers does constitutes a critical range (see the application examples) and (2) the art fails to suggest that short primers (6-8 mers) would be desirable in a dried primer system.

ii. Applicant's examples demonstrate a critical difference in self-priming activity and labeling intensity between 6-8 mers and 9-mers.

iii. While Suganuma suggests that the use of 9-mers or longer reduces the priming efficiency of the random primer reaction because of self-annealing of solution-phase primers, the prior art generally taught that longer primers were generally preferred because longer primers have higher melting temperatures (are more specific).

iv. Even if it is accepted that Suganuma suggests the use of shorter primers in kits comprising primers in solution (and it does not) there is no reason to believe that shorter primers would be advantageous in freeze-dried kits in which the primers are inherently more stable.

v. Suganuma fails to make any disclosure regarding dried reagents and Shen, which discloses 48-mer and 22-mer primers (Example 1 and SEQ ID NOS 1 AND 2), fails to suggest that dried primers should be shortened or any reason why the primers of Suganuma should be dried much less why dried 6-8 mers would be superior to dried 9-mers.